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A Schizophrenia-Susceptibility Locus at 6q25, in One of the World's Largest Reported Pedigrees

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We have completed a genome scan of a 12-generation, 3,400-member pedigree with schizophrenia. Samples from 210 individuals were collected from the pedigree. We performed an "affecteds-only" genome-scan analysis using 43 members of the pedigree. The affected individuals included 29 patients with schizophrenia, 10 with schizoaffective disorders, and 4 with psychosis not otherwise specified. Two sets of white-European allele frequencies were used—one from a Swedish control population (46 unrelated individuals) and one from the pedigree (210 individuals). All analyses pointed to the same region: *D6S264*, located at 6q25.2, showed a maximum LOD score of 3.45 when allele frequencies in the Swedish control population were used, compared with a maximum LOD score of 2.59 when the pedigree's allele frequencies were used. We analyzed additional markers in the 6q25 region and found a maximum LOD score of 6.6 with marker *D6S253*, as well as a 6-cM haplotype (markers *D6S253–D6S264*) that segregated, after 12 generations, with the majority of the affected individuals. Multipoint analysis was performed with the markers in the 6q25 region, and a maximum LOD score of 7.7 was obtained. To evaluate the significance of the genome scan, we simulated the complete analysis under the assumption of no linkage. The results showed that a LOD score >2.2 should be considered as suggestive of linkage, whereas a LOD score >3.7 should be considered as significant. These results suggest that a common ancestral region was inherited by the affected individuals in this large pedigree.

Introduction

Mapping disease loci that predispose to mental disorders is difficult because of several obstacles, including non-Mendelian inheritance, phenotype definition, and gene and allele heterogeneity. One way to overcome these barriers is to study a single extended pedigree. The present study considers one of the world's largest reported pedigrees with individuals suffering from schizophrenia (MIM 181500). The pedigree has been traced back to the 17th century and comprises ~3,400 individuals spanning 12 generations. Here we report a complete genome scan for 43 affected individuals and 167 close relatives collected from the pedigree (in fig. 1, genotyped individuals are indicated by gray boxes). Genotyping was done with 371 markers. Four different phenotypic criteria were used for the linkage analysis: (i) schizophrenia only (Scz); (ii) schizophrenia and schizoaffective depressed type (SAD); (iii) schizophrenia, schizoaffective depressed type, and psychosis not otherwise specified (NOS) (Brd1); and (iv) all the previously mentioned diagnoses and schizoaffective bipolar type (Brd2). Only the affected members of the pedigree were included in the LOD-score calculations. A caveat for our analysis is that, in a large pedigree such as that presented here, it is not possible to type all individuals from all generations to accurately determine the phase for all alleles. Therefore, it is important to estimate accurate allele frequencies for the linkage analysis (Boehnke 1991; Ott 1992; Freimer et al. 1993; Nechiporuk et al. 1993). To tackle this problem, we generated two sets of Swedish allele frequencies. The first set of allele frequencies was obtained from 46 unrelated individuals from the same geographic area (i.e., northern Sweden) inhabited by the pedigree; this group was used because a control sample from northern Sweden would tend to allow reliable estimation of the frequencies of common alleles present in the pedigree. The second set of allele frequencies used was derived from the pedigree, including all affected and unaffected individuals (210 individuals); this group is biased toward a false-negative result both because it includes a large number (i.e., 43) of sick individuals and because the penetrance of the putative schizophrenia

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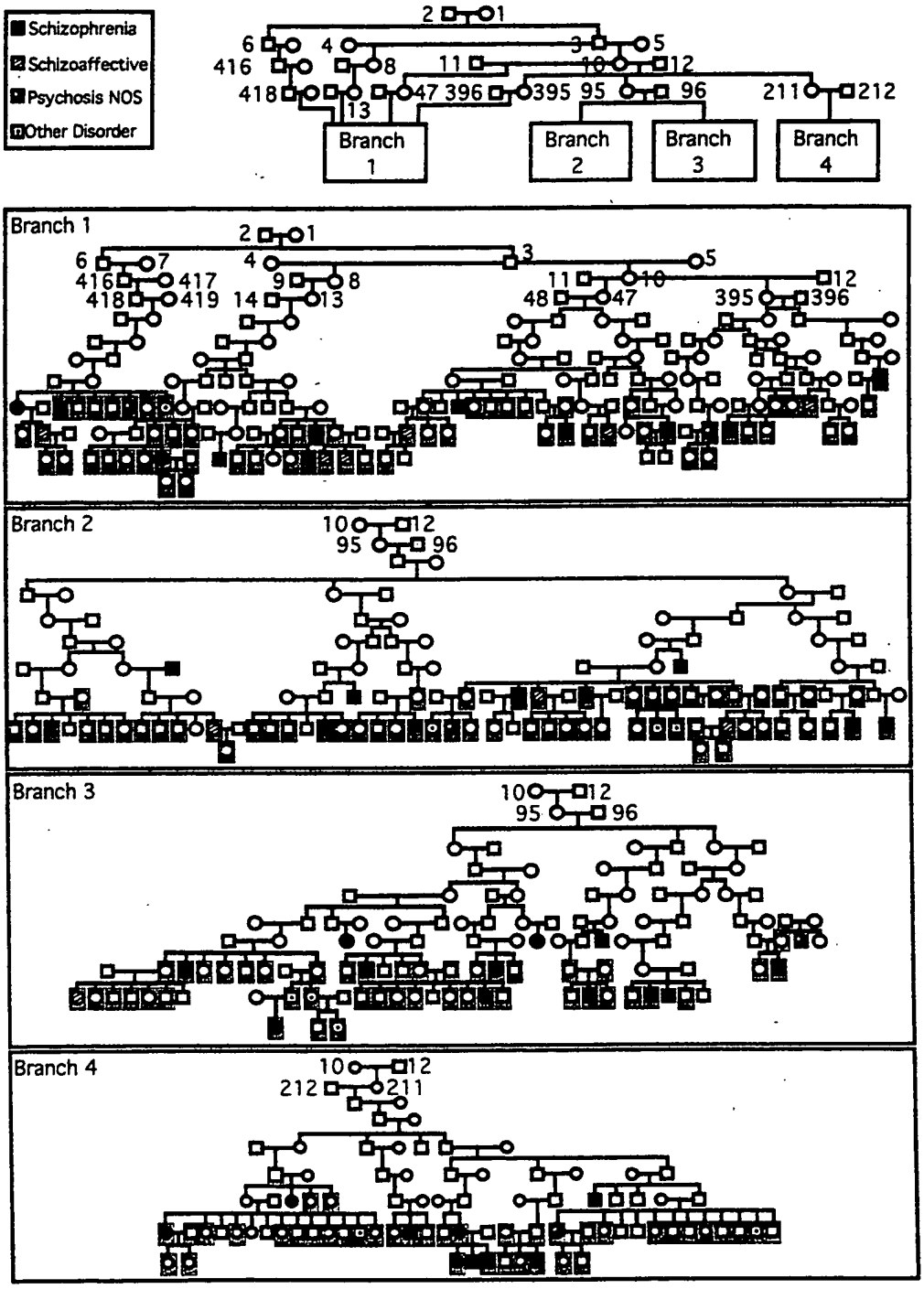

Figure 1 Summary drawing of a large pedigree with schizophrenia, from northern Sweden. The total pedigree consists of 3,400 individuals, 520 of whom are shown. The branches drawn were selected because they contain affected individuals who have given consent to be included in the genome scan and their closest relatives. The upper part of the pedigree, drawn in black, shows the first generations in the 17th century and the connections between the four branches drawn below. We have obtained blood samples from and have genotyped all the 210 individuals indicated by gray boxes. For simplicity, deceased individuals are not indicated.

gene is not known. Our analysis revealed, at 6q25, a candidate schizophrenia-susceptibility locus, which was investigated by a fine-mapping strategy.

Subjects, Material, and Methods

Pedigree Construction and Clinical Assessment

A pedigree consisting of 3,400 individuals spanning 12 generations was constructed on the basis of church records, old psychiatric records, national registers, and information from a Ph.D. thesis (Sjögren 1935). All 43 patients included in the genome scan received, before the start of the project, diagnoses within the "core spectrum of schizophrenia"—that is, Scz, schizoaffective psychosis, or psychosis not otherwise specified, according to DSM-III-R and/or the ICD-9 diagnostic systems. The original diagnosis and the number of previous hospitalizations were obtained from the official Swedish inpatient psychiatric register. The patients were contacted again after 1994 and were asked to participate in the project. From 1994 to 2000, 34 of the 43 patients were interviewed again. Of these 34 patients, 26 were interviewed by means of the Swedish version of the Diagnostic Interviews for Genetic Studies (DIGS) (Nurnberger et al. 1994); for the other 8 patients, a reliable and complete DIGS analysis was not possible, because of their psychiatric condition at the time of the interview. The remaining 9 of the 43 patients could not be interviewed again. Of these 9 patients, 6 died after the collection of blood samples, and 3 could not be assessed, because of either dementia (1 case), deafness (1 case), or stroke (1 case). For the 17 cases for which a complete DIGS analysis was not done after 1994, information from psychiatric unstructured interviews, psychiatric records, clinicians, and interviews with first-degree relatives, by means of the Family Interview for Genetic Studies (FIGS) (Nurnberger et al. 1994), was considered sufficient for confirmation of the official clinical diagnosis. The relatives of affected individuals were interviewed face-to-face and/or over the telephone. The phenotypes of the relatives were considered as "unknown" for the statistical analysis. All clinical data obtained after 1994, including those from DIGS, unstructured interviews, psychiatric records, and FIGS, were added to the Swedish version of the OPCRIT 3.3 (Operational Criteria Checklist) (McGuffin et al. 1991). After 1994, all 43 affected individuals received DSM-IV and OPCRIT diagnosis, with the following distribution: Scz (29 cases); schizoaffective disorder, depressed type (6 cases), schizoaffective disorder, bipolar type (4 cases); and NOS (4 cases). The OPCRIT-based diagnosis and the DSM-IV–based diagnosis were in full agreement. All diagnoses were established by two psychiatrists independently. The patients included 21 females with a mean age, at the time of the blood extraction, of 55 years (54.9 ± 15.5 years) and a mean age at onset of about 27 years (26.6 ± 8.9years). The 22 males had a mean age of ~50 years (50.4 ± 15.2 years) and a mean age at onset of ~24 years (24.2 ± 7.3 years).

Blood was collected from the 43 affected individuals and their closest relatives, resulting in a total of 210 blood samples that were included in the genome scan (see fig. 1, where genotyped individuals are indicated by gray shading). The collection of all the blood samples was done by the Research Unit at the Department of Clinical Sciences, Division Psychiatry, at Umeå University in Sweden.

Genotyping

We used 371 polymorphic microsatellite markers. Information about many of the primers used for genotyping and about sequences, heterozygosity, and allele sizes were obtained from The Genetic Location Database (Collins et al. 1996) and The Genome Database. The information for some additional, improved markers, as well as linkage-map information on the markers used was extracted from the databases at Axys Pharmaceuticals. The average marker spacing in the genome scan was ~10 cM. There were eight gaps >30 cM; these gaps do not correspond to regions previously suggested to contain schizophrenia loci. The alleles for the markers were assigned by means of an approach for high-throughput genotyping (Hall et al. 1996). Multiple aliquots of the DNA extracted from the 210 individuals, with a concentration of 4 ng/ml, were dried in multiple 96-well replica plates. PCR mixing and the dispensing of mixes into the 96-well plates with the patients' DNA were performed by a Packard Robotic System Multiprobe 204 (Packard Instruments). Each PCR reaction was 20 μl, containing 2 μl of 10 mM dNTP, 2 μl of 10 × PCR buffer, and 1 μl 50 of mM $MgCl_2$. The DNA was subject to PCR in a MJ PTC-100 ™ (MJ Research). Markers were amplified separately, and then 8-16 markers were pooled according to panel-set category. Pooling was performed by a CRS/MultiPette Work Cell (CRS Robotics). The pooled samples were then loaded onto an ABI 373 or an ABI 377 (Applied Biosystems), depending on the resolution necessary for the markers. Thirty-three panel sets resulted in a total of 371 markers. The results were analyzed by GENOTYPER version 2.1 (Applied Biosystems). An additional genome scan was performed, with the same 371 markers, on 46 healthy individuals originating from the same geographic area inhabited by the pedigree. This was done to obtain allele frequencies in the Swedish control population, to be used in the linkage analyses.

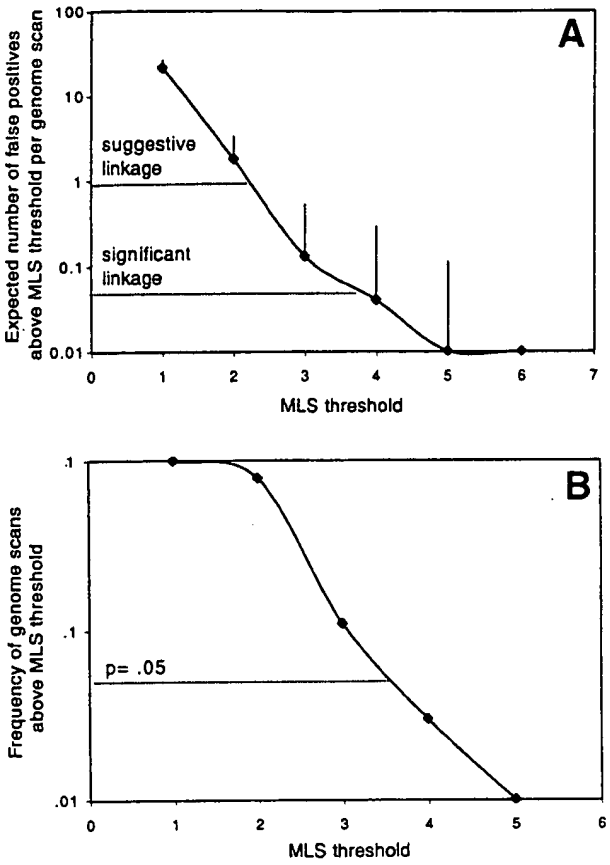

Figure 2 Genomewide simulation analysis. The upper graph shows the number of expected MLS values at or above a given MLS threshold, under the assumption of no linkage. This is equivalent to the average number of expected false-positive hits at or above each threshold, plotted on a logarithmic scale. Suggestive MLS values (1 false-positive per genome scan) and significant MLS values (1 false-positive per 20 genome scans) are indicated by, respectively, the upper and lower dotted lines. The lower graph shows the proportion of genome scans exceeding each MLS value, plotted on a logarithmic scale. The dotted line represents the $P = .05$ level.

Statistical Analysis

Four different groups of phenotypic criteria were used in the linkage studies: (i) Scz, (ii) SAD, (iii) Brd1, and (iv) Brd2. Healthy members of the pedigree, as well as individuals with other psychiatric diagnoses, were denoted "phenotype unknown."

We performed a two-point linkage analysis, using the MLINK program from the LINKAGE package (Cottingham et al. 1993). We did not use allele frequencies from The Genome Database, for two reasons: first, The Genome Database frequencies are, in most cases, derived from a relatively small number of chromosomes, which might result in inaccurate frequencies that can give spurious results; second, the analyses of the Swedish control population and of the pedigree were done with the same set of tools, ensuring a correct identification of alleles in both groups. For the calculations, we used the same model that had been presented in our previous replication work on chromosome 6p23 (Lindholm et al. 1999); in brief, a model assuming a dominant trait was used. The sporadic risk was set to 0.4%, the mutation rate was 10^{-6}, and a maximum penetrance of .4 was used (Levinson et al. 1996). To avoid the problem of low penetrance of schizophrenia, only the affected members were included in the calculations. Linkage analyses were also performed with an additional set of allele frequencies. The second set of allele frequencies was obtained from the distribution of alleles in the pedigree analyzed in the genome scan. For saturation mapping, a third set of allele frequencies, from 46 healthy individuals from northern Sweden, was used, depending on the availability of samples at the time for the analysis.

To evaluate the significance of the results, we performed simulations of the complete genome-scan data. This analysis was performed at the PDC (Parallel Data Center) in Stockholm. We simulated the complete genome-scan data, for the two sets of frequencies and four diagnostic groups (eight models), 100 times. For each simulated replicate of the genome scan, we analyzed all markers by means of the eight models. We therefore performed 37,000 simulations and 296,000 LOD-score calculations under the assumption of no linkage. We have reduced the number of alleles for each marker to five. For each marker, we noted both the maximum LOD score (MLS) under each of the eight models and the MLS of all eight models. For all genome-scan replicates, we then calculated, for the eight-model MLS, the average (and SD) number of LOD scores that exceeded each threshold (fig. 2*A*) and the proportion of genome-scan replicates that had at least one LOD score that exceeded each threshold (fig. 2*B*). A *suggestive* LOD-score threshold was considered as being the eight-model MLS value expected once in each genome scan; a *significant* LOD-score threshold was the average eight-model MLS value that would be expected to occur, by chance, once in 20 genome scans. A similar analysis has been published elsewhere (Sawcer et al. 1997).

We performed a three-point linkage analysis, using the FASTLINK program from the LINKAGE package (Cottingham et al. 1993). Seven markers were included in the calculations. The genetic distances were taken from The Genetic Location Database (Collins et al. 1996). The EHPLUS package (Zhao et al. 2000) was used to estimate the difference between the frequency of the 6q25 haplotype in 43 affected individuals and that in 46 unrelated controls.

Results

LOD-score data on the four different diagnostic groups described above (see the Subjects, Material, and Meth-

Table 1

Markers with MLS Values >1.5, for Allele Frequencies in the Swedish Control Population and for Allele Frequencies in the Pedigree, for Four Diagnostic Categories

Chromosome and Marker	Results for Allele Frequencies from Control Population		Results for Allele Frequencies from Pedigree	
	MLS (θ^a)	Diagnosis	MLS (θ^a)	Diagnosis
2:				
D2S337	2.60 (.15)	Scz	.00 (.35)	Scz
D2S151	1.72 (.15)	Scz	.95 (.15)	Scz
D2S125	2.14 (.20)	Brd1	.34 (.30)	Brd2
3:				
D3S1297	1.72 (.15)	Brd1	.01 (.30)	Scz
D3S1304	2.72 (.10)	Brd1	.57 (.20)	Brd2
D3S1263	3.30 (.15)	Brd2	.30 (.25)	SAD
D3S1566	1.76 (.10)	Brd2	.53 (.15)	Brd1
D3S1580	1.55 (.15)	Scz	.18 (.30)	Scz
5:				
D5S419	2.02 (.20)	Brd1	.47 (.20)	Brd2
D5S644	1.82 (.15)	Scz	.49 (.25)	SAD
D5S433	1.59 (.20)	Brd2	.08 (.30)	Scz
6:				
D6S344	3.60 (.05)	Scz	−.03 (.40)	Scz
D6S264	3.45 (.00)	Brd1	2.59 (.00)	Brd1
7:				
D7S636	2.00 (.10)	Scz	.00 (.20)	Scz
8:				
D8S550	2.90 (.15)	Scz	.70 (.15)	Scz
9:				
D9S157	1.72 (.05)	Scz	1.47 (.05)	Scz
D9S175	2.00 (.15)	SAD	.00 (.20)	SAD
D9S299	2.01 (.05)	Brd2	1.11 (.10)	Brd2
10:				
D10S189	1.94 (.10)	Brd2	.38 (.20)	Brd2
11:				
D11S1324	1.74 (.20)	Brd2	−.03 (.40)	Scz
13:				
D13S283	1.66 (.15)	Scz	.65 (.15)	Scz
D13S152	1.58 (.20)	Brd2	.04 (.35)	Brd1
D13S173	1.53 (.10)	SAD	.53 (.15)	SAD
14:				
D14S258	1.60 (.15)	Brd1	.00 (.20)	Brd1
16:				
D16S401	2.52 (.15)	SAD	.23 (.30)	Scz
20:				
D20S118	3.57 (.20)	Brd2	−.12 (.40)	Scz
D20S178	2.70 (.15)	Brd2	.10 (.25)	Brd1
D20S100	1.76 (.10)	Scz	1.37 (.10)	Scz
D20S173	2.39 (.15)	SAD	.05 (.35)	Scz
21:				
D21S266	1.61 (.15)	Scz	.27 (.25)	Scz
22:				
D22S280	1.61 (.15)	Brd2	.09 (.30)	Brd2

NOTE.—The MLS values for marker *D6S264*, which reached suggestive levels of significance in both the Swedish control population and the pedigree, are underlined.

[a] Recombination fraction.

ods section), analyzed by means of allele frequencies in the Swedish control population and in the pedigree, are plotted in figure 3; this figure shows that linkage analyses using allele frequencies in the Swedish control population gave LOD scores >3 with four markers: *D3S1263*, *D6S344*, *D6S264*, and *D20S118*. Of these, only *D6S264* gave LOD scores >2 when allele frequencies in the pedigree were used (fig. 3*B* and table 1). To evaluate the significance of the results, we performed a complete simulation of the genome scan, using all models to calculate empirical LOD scores for the pedigree, under the assumption of no linkage. We have reduced the number of alleles for each marker to five. We performed 37,000 simulations (370 markers simulated 100 times each) and 296,000 LOD-score calculations (each of the simulated pedigrees was subjected to eight LOD-score calculations, for all combinations of allele frequencies and diagnostic groups). These simulations indicated that, for the pedigree structure and models used in the present study, a LOD score >2.2 should be considered as suggestive whereas a LOD score >3.7 should be considered as significant (fig. 2). Table 1 shows that nine markers included in the genome scan produced LOD scores higher than the suggestive value of 2.2: markers *D2S337*, *D3S1304*, *D3S1263*, *D6S344*, *D6S264*, *D8S550*, *D16S401*, *D20S118*, and *D20S173*. Table 1 also includes additional markers with LOD scores >1.5, for comparisons with other studies. All nine markers that produced suggestive linkage results were selected for further studies. Flanking markers on each side of these markers were typed. The results supported only the positive linkage for *D6S264*. Two-point LOD scores for six additional markers located close to *D6S264* are shown in figure 4. A two-point MLS of 6.6 was obtained with *D6S253* (marked by an arrow in fig. 4). Figure 4 also shows haplotypes in the 6q25 region, constructed for all affected individuals whose parents were available. For 19 affected individuals connected to the same ancestor nine generations back, we were able to determine the phase and the haplotype inherited from the pedigree; 11 of these 19 patients shared a 6-cM haplotype (*D6S253–D6S264*), and 7 of the 19 patients shared a part of this haplotype.

We also conducted three-point analysis of the seven markers in the 6q25 region, using allele frequencies in the Swedish control population, and we found an MLS of 7.7 between markers *D6S253* and *D6S297* (fig. 5).

Discussion

We have conducted a genomewide screening of a very large schizophrenia pedigree from northern Sweden, and we have found, at 6q25, a candidate schizophrenia-susceptibility locus. To evaluate the significance of the results, the calculations should be corrected for the fact

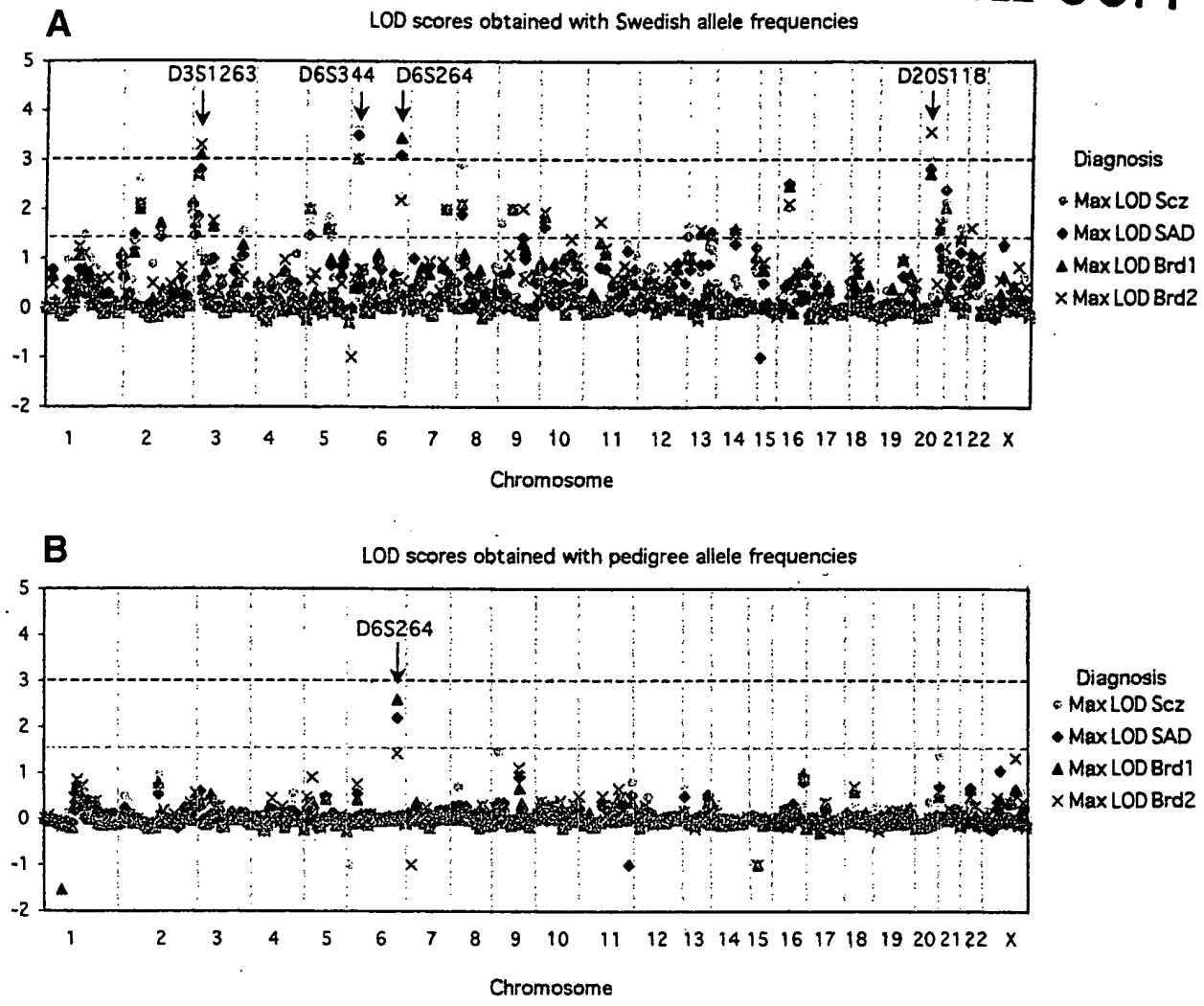

Figure 3 Plot of genome-scan data on 371 markers, using four diagnostic criteria and two sets of allele frequencies. The MLS for each marker is plotted for allele frequencies in the Swedish control population (*A*) and in the pedigree (*B*). Each panel includes one plot for each of the four diagnostic categories used (four plots per panel): Scz, SAD, Brd1, and Brd2. The plotted values for the LOD scores >3 are indicated by an arrow and the marker name. The scale for each chromosome reflects the number of markers typed, rather than the size of the chromosome.

that we performed multiple tests. A very stringent correction would be to decrease the value of all the LOD scores by log(8) = 0.9, since we have used four types of diagnosis and two sets of allele frequencies. This correction, which would render all of our reported LOD scores as not significant, is not very appropriate, since the four phenotypes are correlated. As an alternative, we performed a complete simulation of the genome scan, using all eight models to calculate empirical LOD scores for the pedigree, under the assumption of no linkage. These simulations indicated that, with the pedigree structure and models used in the present study, a LOD score >2.2 should be considered as suggestive whereas a LOD score >3.7 should be considered as significant. As mentioned above, the highest linkage value in the genome scan was reached with marker *D6S264* on chromosome 6q25 (table 1). The results for this marker reached suggestive values of significance, according to our simulation studies. The fact that *D6S264* was the only marker that gave consistent results with the two sets of allele frequencies further strengthens the significance of these results.

Additionally, *D3S1263* located on 3p25, *D6S344* located on 6p24, and *D20S118* located on 20p11.2 showed the highest suggestive values (MLSs of 3.30, 3.60 and 3.57, respectively). Marker*D6S344* gave an MLS of 3.6. This marker is located on 6p24, a region that others (Straub et al. 1995; Schizophrenia Linkage Collaborative Group for Chromosomes 3, 6 and 8 1996; Turecki et al. 1997; Nurnberger and Foroud

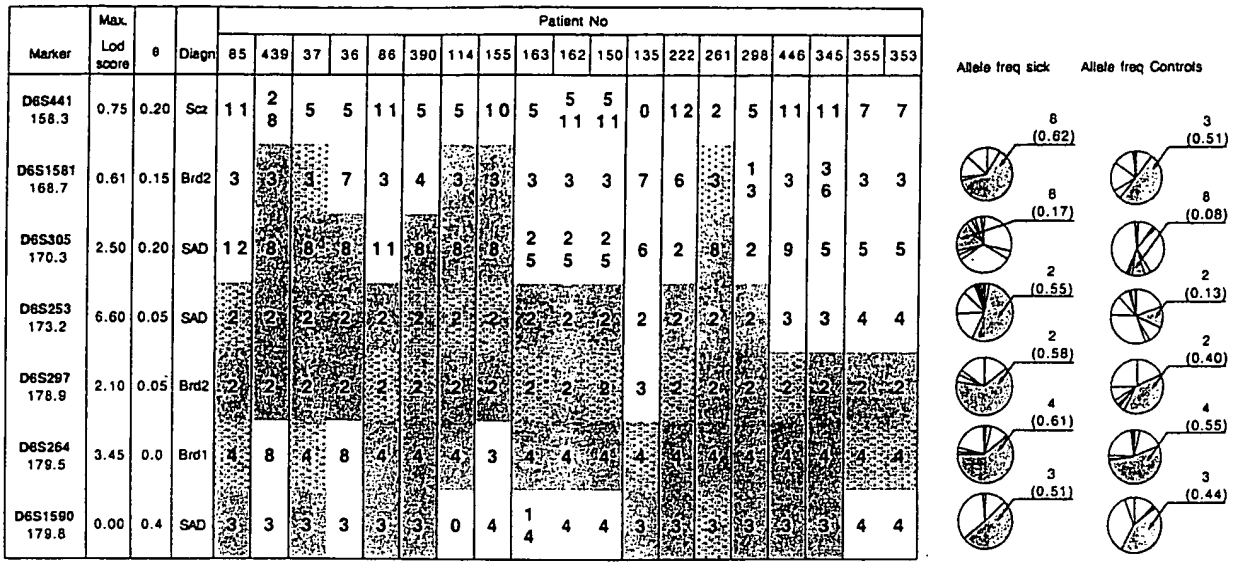

Figure 4 Haplotype analysis of the 6q25 region. In the table, a haplotype (indicated by gray shading) close to marker *D6S264* is shown, for 19 affected individuals whose phase is known. Only the haplotype that is transferred from the pedigree (and not from the in-married parent) is shown. For the individuals in whom a marker was uninformative, the allele included in the haplotype is indicated by stippling. Both alleles are indicated for genotypes for which phase is unknown. Haplotypes from siblings are not separated by a vertical black line. The tale also shows, for each marker, the LOD score, the recombination fraction (θ), and the diagnosis that gave the MLS. The circles to the right of the table show allele frequencies in affected individuals and in the Swedish control population. Alleles that are represented in the haplotype are indicated by gray shading.

1999) have suggested as containing a schizophrenia-susceptibility locus. In fact, we elsewhere have published a part of the 3,400-member pedigree (i.e., ~2,000 members), in an attempt to replicate findings for chromosome 6p (Lindholm et al. 1999). *D6S344* is located ~2 cM from marker *D6S277*, contained in a haplotype that was found to segregate with the disease in a small branch of the pedigree (Lindholm et al. 1999); however, one possibility is that *D3S1263* (LOD score 3.3), *D6S344* (LOD score 3.6), and *D20S118* (LOD score 3.6) are false-positive results, since the calculations were not consistent for both sets of allele frequencies. The results stress the importance of an accurate evaluation of allele frequencies used in the analysis of extended pedigrees. Another possibility is that there is heterogeneity inside the pedigree, with one or more of these markers segregating with a schizophrenia locus in just one part of the pedigree.

LOD scores were calculated for additional markers in the 6q25 region, and several of them reached suggestive or significant values, as shown in figure 4. One problem in this region is that the alleles present in the haplotype segregating in the pedigree are frequent in the Swedish control population, a finding that decreases their informativeness for LOD-score calculations (in fig. 4, circles represent allele frequencies in the affected individuals in the pedigree and in a Swedish control population). However, marker *D6S253* (indicated by an arrow in fig. 4), which has a more-even allele distribution, resulted in an MLS of 6.6. According to the three-point analysis (fig. 5), it is possible that a schizophrenia-susceptibility gene is located in the region between markers *D6S253* and *D6S297*, a region that reached an MLS of 7.7. The haplotypes shown in figure 4 supports this finding, except in the case of patient 135; it is possible that allele 2 for marker *D6S297* has mutated to allele 3 in this individual; an alternative explanation is that this individual is a phenocopy. All other individuals have either the complete haplotype (11 of 19 patients for whom we could determine haplotypes) or part of it (7 of 19 patients). We were not able to collect, for haplotype analysis, all the parents of the 43 affected individuals. Therefore, we used the EHPLUS package (Zhao et al. 2000) to estimate the frequency of the *D6S253* (allele 2)–*D6S297* (allele 2)–*D6S264* (allele 4) haplotype in the 43 affected individuals from the pedigree versus that in 46 unrelated controls. We found a significant increase in the frequency of this 6-cM haplotype in the pedigree compared with the controls: empirical $P = .004$ for a model-free analysis; in light of the frequency of the haplotype in the normal population, this P value indicates a significant probability that this region has been inherited by the affected individuals IBD. This result suggests that the increase

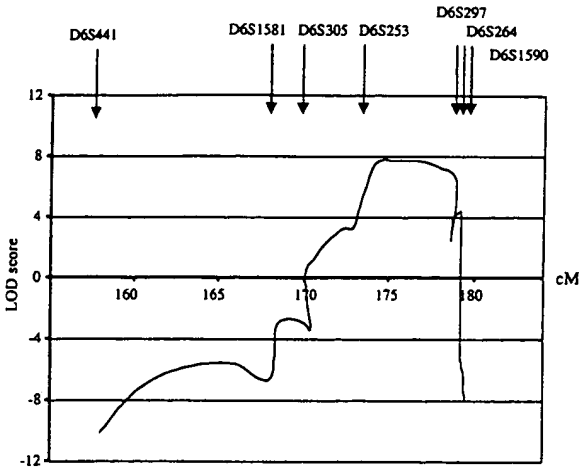

Figure 5 Multipoint analysis of the markers in the 6q25 region, performed by use of diagnostic category Brd1 and allele frequencies in the Swedish control population. Three-point LOD scores were calculated and plotted against the distance (in cM) from the p-terminal. The MLS was obtained between markers *D6S253* and *D6S297* and reached a value of 7.7.

in haplotype frequency in the pedigree is not due to a common frequency of this region in the Swedish population. In conclusion, the EHPLUS analysis further strengthens the possibility that this region segregates with the disease in the large pedigree.

Previous schizophrenia genome scans have proposed schizophrenia-susceptibility loci on 1q, 2q, 3p, 4q, 5p, 5q, 6p, 7q, 8p, 9q, 10p, 10q, 11q, 13q, 22q, and Xp (Lasseter et al. 1995; Pulver et al. 1995; Straub et al. 1995, 1997, 1998; Gill et al. 1996; Blouin et al. 1998; Crowe and Vieland 1998; Levinson et al. 1998; Brzustowicz et al. 1999, 2000; Hovatta et al. 1999; Nurnberger and Foroud 1999; Ekelund et al. 2000). Two of these genome scans reported significant linkage results (Blouin et al. 1998; Brzustowicz et al. 2000). These two studies used dominant and recessive models for the segregation analysis. In the present study, we used only a dominant model, because we considered a dominant segregation to be more likely in the large pedigree. The analysis of only a dominant model decreases the risk of type 1 errors. The studies by Blouin et al. (1998) and Brzustowicz et al. (2000) included the analysis of multiplex families, whereas the present study includes a single large pedigree. The analysis of a single pedigree decreases the probability of heterogeneity and increases the chance of finding a single gene of major effect. Multiple susceptibility loci are most probably involved in the etiology of schizophrenia, and the fact that these three studies report different loci is not surprising.

Until now, a schizophrenia locus at 6q25 had not been described; however, a 6q position closer to the centromere has been proposed to contain a schizophrenia-susceptibility locus (Cao et al. 1997; Kaufmann et al. 1998; Martinez et al. 1999). In fact, excess allele sharing has been reported for markers in the 6q13-26 region (Cao et al. 1997; Kaufmann et al. 1998); however, the 6q23-q26 region was excluded in a follow-up multicenter study, and only 12 microsatellite markers spanning 6q13-q23 were investigated (Martinez et al. 1999). The 6q23-q26 region was most likely excluded because the *P* values for the markers in this region were lower than those for the markers on 6q13-q23. The possibility remains that all the studies of the 6q region describe a single schizophrenia locus.

Interestingly, an autism-susceptibility locus also has been mapped to the 6q25 region (Philippe et al. 1999), and deletions of the 6q25 segment can result in developmental problems and anomalies of the brain (Sukumar et al. 1999). These results suggest that genes important for normal brain function and development are located on 6q25.

In summary, we have analyzed the world's largest reported pedigree with individuals affected with schizophrenia and have found a candidate schizophrenia-susceptibility locus at 6q25. The fact that the 6q locus reached one of the highest LOD scores reported so far warrants further investigations of this region, in other families around the world.

Acknowledgments

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Electronic-Database Information

The accession number and URLs for data in this article are as follows:

Genetic Location Database, The, http://cedar.genetics.soton.ac.uk/public_html/ldb.html (for primers used for genotyping, sequences, heterozygosity, and allele sizes)

Genome Database, The, http://www.gdb.org/ (for primers used for genotyping, sequences, heterozygosity, and allele sizes)

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for schizophrenia [MIM 181500])

PDC (Parallel Data Center [Center for Parallel Computers, KTH]), http://www.pdc.kth.se

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